PCT/EP 00/06545

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Dated 25 May 2000

Patents Form 1/77

Patents Act 1977
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The Patent Office

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(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — P77426 GCW CMK

9916882.5

2. Patent application number
(The Patent Office will fill in this part) — 15 JUL 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — PHARMACIA & UPJOHN SPA
VIA ROBERT KOCH 1.2
20152 MILAN

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — ITALY

4. Title of the invention — ANTITUMOR SYNERGISTIC COMPOSITION

5. Name of your agent *(if you have one)* — J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — 14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d)) — YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	4
Claim(s)	2
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	2 x 5
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature [signature] Date 19 July 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS C.M. KEEN
0171 405 3292

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

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d) *If you have answered "Yes" Patents Form 7/77 will need to be filed.*

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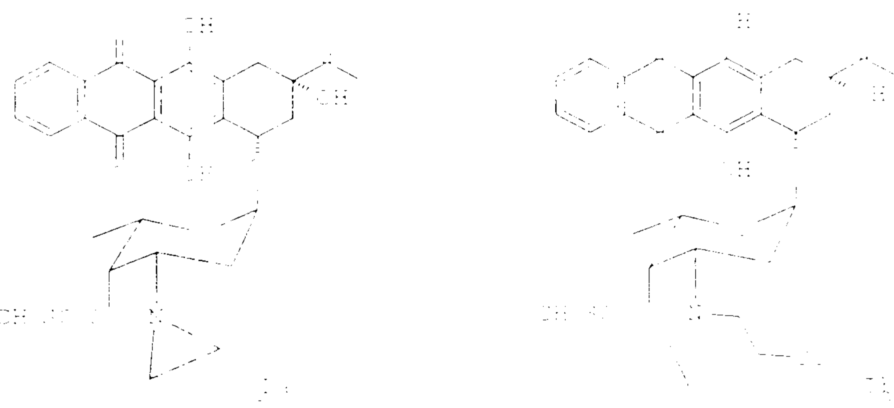
Antitumor Synergistic Composition

The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and an antimetabolite compound, having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising:

- an alkylating anthracycline of formula Ia or Ib:



Ia Ib

- an antimetabolite compound, and a pharmaceutically acceptable carrier or excipient.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design [illegible], vol. [illegible], [illegible], and claimed respectively in US-A-[illegible] and US-A-[illegible]. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N7 position in DNA minor groove via their alkylating moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

Antimetabolites are described in various scientific publications. The main representatives of this wide class of drugs are: the antifolates such as methotrexate, raltitrexed and trimetrexate ; the 5-fluoropyrimidine compounds such as 5-fluorouracil, floxuridine and capecitabine; the cytidine analogs like cytarabine, azacitidine and gemcitabine. See for example the review: Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 432-450. The 5-fluoropyrimicine compounds and the cytidine analogs are the preferred antimetabolite compounds to be used in the present invention, more preferably 5-fluorouracil or gemcitabine. The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, as combined preparation for simultaneous, separate or sequential use in antitumor therapy. A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, in amounts effective to produce a synergistic antineoplastic effect. The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antimetabolite compound as defined above and an alkylating anthracycline of formula Ia or Ib, as defined above, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a antimetabolite compound to mammals, including human.

by the term "parenteral" or "administering" as used herein is meant intravenous, intramuscular and intraperitoneal administration. By "intravenous" is meant intravenous, intramuscular and intraperitoneal administration. In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the antimetabolite compound, or the compound may be administered sequentially, in either order. It will be appreciated that the actual preferred method and sequence will vary according to, inter alia, the particular formulation of the alkylating anthracycline formula Ia or Ib being utilized, the particular formulation of the antimetabolite compound, such as one of the 5-fluoropyrimidine or cytidine class, being utilized, the particular tumor to be treated, and the particular host being treated.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 100 mg/m² of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m² of body surface area.

In the method of the subject invention, for the administration of the antimetabolite compound the course of therapy generally employed is from about 0.1 to about 1 g/m² of body surface area. More preferably, the course therapy employed is from about 1 mg/m² to about 1 g/m² of body surface area. The antineoplastic therapy of the present invention is in particular suitable for treating breast, ovary lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an effective amount of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound in the prevention or treatment of metastasis or in the treatment of

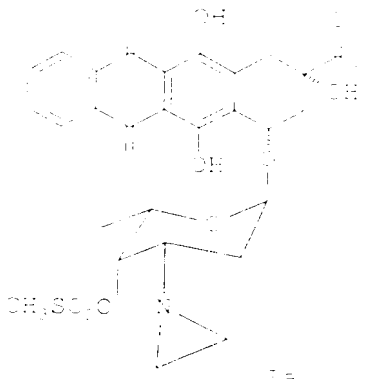
tumors by angiogenesis inhibition, as well as to the use of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis .

As stated above, the effect of an alkylating anthracycline of formula Ia or Ib and an antimetabolite compound, such as a 5-fluoropyrimidine or cytidine derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracyclines and of the antimetabolites and thus yields the most effective and least toxic treatment for tumors.

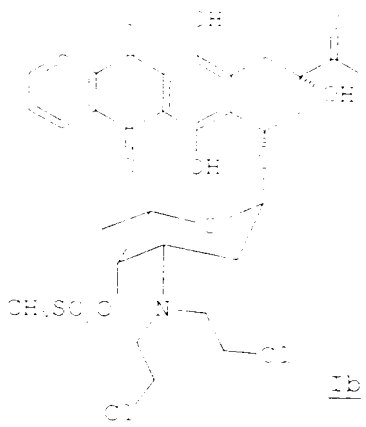
The superadditive actions of the combination preparation of the present invention may be shown for instance by in vivo tests for the antileukemic activity on disseminated L1210 murine leukemia. The combination of Ia with 5-Fluorouracil or gemcitabine, tested at the different doses and schedules, produces favorable ILS% values [Increase in life span: [(median survival time of treated mice/median survival time of controls)x 100]-100), indicating a synergistic effect. For these experiments Ia was solubilized in [Cremophor /EtOH = 6.5:3.5]/[normal saline]=20/80 v/v, while standard pharmaceutical preparation were used for the antimetabolite compounds.

Claims

1. A product containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antimetabolite compound as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. A product according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin.

3. A product according to claim 1 or 2 wherein the antimetabolite compound is a cytidine analog.

4. A product according to claim 1 or 2 wherein the antimetabolite compound is a 5-fluoropyrimidine.

5. A product according to claim 3 wherein the cytidine analog is gemcitabine.

6. A product according to claim 4 wherein the 5-fluoropyrimidine is 5-fluorouracil.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound.

8. A composition according to claim 7 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the treatment of tumors.

10. Use according to claim 8 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

11. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

ABSTRACT

Antitumor Synergetic Composition

The combination of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methanesulfonyl daunorubicin and an antimetabolite compound in the treatment of tumors, especially in the treatment or prevention of metastasis in the treatment of tumors by the inhibition of angiogenesis.